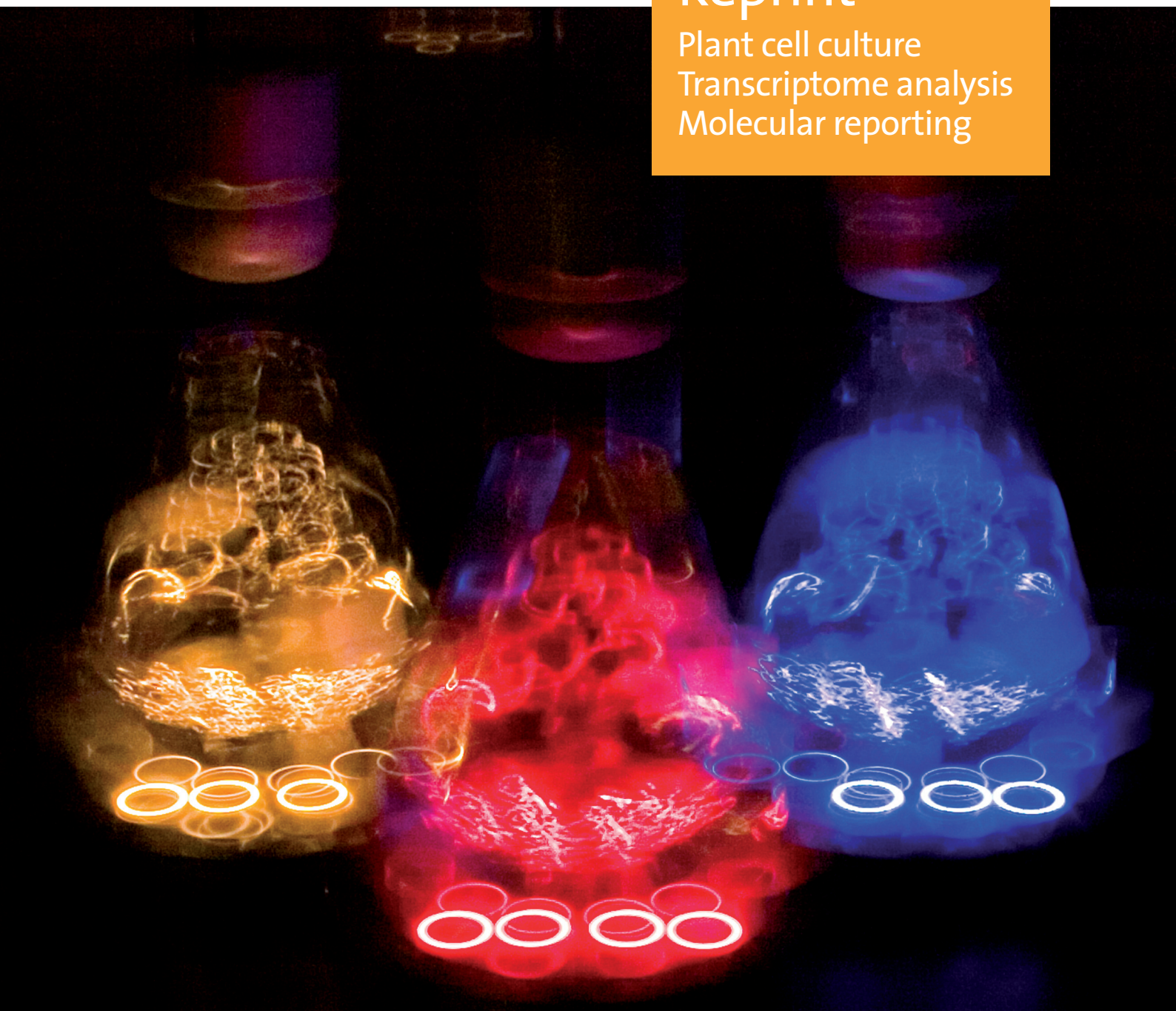
ISSN 1860-6768 · BJIOAM 7 (4) 465 – 584 (2012) · Vol. 7 · April 2012

Biotechnology Journal

Systems & Synthetic Biology · Nanobiotech · Medicine

Reprint

Plant cell culture
Transcriptome analysis
Molecular reporting



www.biotechnology-journal.com

WILEY-BLACKWELL

Biotech Highlight

The structuring of GMO release and evaluation in EU law

Caroline von Kries[1] and Gerd Winter[2,3]

[1] LL.M (Lund), Attorney at Law, Freiburg/Br., Germany
[2] Center for European Environmental Law (FEU), University of Bremen, Bremen, Germany
[3] Faculty of law, University of Bremen, Bremen, Germany

Received 28 JUN 2011
Revised 12 AUG 2011
Accepted 20 SEP 2011

Keywords: Biosafety · Genetically modified organisms · GMO regulation · Risk assessment

1 Introduction

Genetically modified organisms (GMOs) and their behaviour in the environment are complex and can only be assessed if the different components are distinguished, individually analysed and then again viewed in their entirety. Similarly, the investigating grasp of risk assessment – as an intellectual process – is complex and can only develop if it proceeds in well-ordered steps, which are then synthesized in an appropriate manner. The components of GMO release (object) and its examination (assessment) may be distinguished as shown in Table 1.

This essay examines how the law structures the double complexity by drawing distinctions, selecting the most relevant issues and bringing them to the attention of the applicants and competent authorities. It should be noted from the outset that the law does not determine every detail but recognizes that risk assessment is primarily an operation in the realm of scientifically informed administrative bodies. In legal terms, the relevant law is interpreted for granting discretionary margins of assessment by the relevant administrative authority [1]. However, this does not allow arbitrary conduct. Rather, the competent authorities must observe the legal structuring of the complexity of the GMO release and examination, consider all scientifically justifiable knowledge and respect any substantive legal standard.[1]

Correspondence: Prof. Gerd Winter, Faculty of Law, University of Bremen, Universitätsallee, GW 1, 28359 Bremen, Germany
E-mail: gwinter@uni-bremen.de

Abbreviations: EFSA, European Food Safety Agency; **ERA**, environmental risk assessment; **GM**, genetically modified; **GMO**, GM organism

2 Dimensions of GMOs and their behaviour

A GMO introduced into the environment will affect many different environmental and societal endpoints and do this through a large variety of causation processes that unfold on various levels of organismic interaction. The law selects the endpoints that are to be protected and determines what causation processes and levels need to be checked.

2.1 Protected endpoints

2.1.1 Human health and the environment

EU legislation categorises the introduction of GMOs into the environment as the deliberate release at a particular site and the introduction into the environment at any site after GMOs have been placed on the market.[2] These introductions are starting points for potential paths of risk emergence, which finally may collide with certain endpoints. The law determines which endpoints are worth protecting and – by implication – which not.

[1] Traditionally, the Anglo-Saxon test of "arbitrariness and capriciousness" has left more ample room for administrative discretion than the German dense judicial review, which has endowed the judge with quasi-administrative powers. More recently, both systems appear to approach each other, with the Anglo-Saxon doctrine judicialising and the continental doctrine recognising discretionary margins. They tend to converge by restricting discretion more or less in the way stated in the text. This shows a comparison of court reasoning, for instance of Geertson Seed Farms Inc vs Johanns 2007 WL 518624, 2007 WL 1302981 (ND Cal) for the US, of Downs vs Secretary of State [2009] EWCA Civ 664 for the UK and of Higher Administrative Court (OVG) Berlin of 9. 7. 1998 – OVG 2 S 9.97, in: Eberbach/Lange/Ronellenfitsch, Gentechnikrecht, Biomedizinrecht. Entscheidungen. Ch. 10 on § 16 GenTG, No. 40 for Germany.

[2] Parts B and C of Directive 2001/18/EC of the European Parliament and the Council of 12 March 2001 on the deliberate release into the environment of GMOs [...], O.J. L 106 of 14.4.2001, p. 1.

Biotechnol. J. 2012, 7, 569–581

Table 1. Structuring the complexity of GMO release and examination

Dimensions of the object	Dimensions of the assessment
● Endpoints of protection ○ human beings ○ environment ○ coexistence ○ economic costs ○ economic benefits ○ political/ cultural values ● Paths of impact ○ direct/indirect ○ short/long term ○ cumulative ● Biological levels ○ molecular ○ cellular ○ organismic ○ organismic interaction ○ ecological ● Causes ○ entire GMO ○ transgene	● Knowledge generation ○ closed systems ○ deliberate release ○ placing on the market ○ monitoring ● Knowledge supply ○ applicant ○ authority ○ science ● Risk assessment ○ hazard ○ magnitude of effects ○ likelihood of effects ○ linking likelihood with magnitude ○ management strategies ○ overall risk determination

EU law has established that the protected goods are human health and the environment. These have to be kept safe from 'adverse effects'. 'All appropriate measures' must be taken to prevent such effects.[3] These measures will normally be determined by the conditions of an authorisation. If they are not sufficient to prevent adverse effects, the project fails to meet the core precondition of the authorisation, which must therefore be denied.

2.1.2 Socio-economic costs

EU legislation on genetic engineering does not mention socio-economic costs of GMO release as a concern. By contrast, Art. 1 No. 1 of the German Gene Technology Act (GenTG) protects, apart from human beings and the environment, material assets, which includes, for instance, damage to crops on neighbouring fields. However, if one interprets the EU legal term 'environment', drawing on the EU directive on environmental impact assessment as seems appropriate, material assets are also protected under European law.[4] The protected object 'material assets' is especially relevant when it comes to the coexistence of organic, conventional and GMO cultivation. In this context, the material goods are the plant population and the business of an organic or conventional farmer, the adverse effect being the transfer of transgenes to plants and the resulting socio-economic loss.

The mere presence of a transgene in non-GM agricultural product is not per se considered as adverse effect by court practice and legal scholars. They posit the adverse effect must follow from such presence, like the damaging of a non-target species by an insecticide plant. The justification given is that the law only addresses the specific risks of genetic engineering, which are only health and environmental risks.[5] This reasoning can, however, be countered by the fact that the safeguarding of coexistence – and hence the prevention of transfer per se of transgenes to other plants – has been made a legitimate object of protection under both European and a Member State legislation.[6] This also implies that the restricted marketability of a product as GM-free has to be considered as damaging to a protected material asset.[7] Consequently, in the authorisation procedure for deliberate releases, whether adequate isolation distances exist between neighbouring sites cultivating GMOs and non-GMOs has to be examined. By contrast, in the procedure of authorising the placing of GMOs on the market, where the precise location of introduction is not yet known, coexistence cannot be checked (except in the sense of giving the all-clear if the GM crop has heavy pollen that does not travel far, is sterile or is a strong self-pollinator). In these cases, measures preventing transfers of genes can only be taken following the authorisation for the placing on the market.

2.1.3 Socio-economic benefits

GMO releases may create benefits for the producer and consumer. Is this to be weighed against the risks to human health, the environment and the socio-economic welfare of the non-GMO farmer?[8] Such an analysis is envisaged in the genetic engineering legislation of some countries.[9] It is, however, largely

[3] Art. 4 Directive 2001/18/EC. Regulation (EC) 1829/2003 of the European Parliament and the Council of 12 March 2001 on genetically modified food and feed, O.J. L 268 of 18.10.2003, p. 1 in Art. 4 (1) mentions animals in addition to humans and the environment because it also covers feed.

[4] Art. 3 Directive 85/337/EEC lists as „factors" of the environment human beings, fauna and flora, soil, water, air, climate, landscape, material assets and the cultural heritage.

[5] See for Germany Administrative Court (VG) Berlin, decision of 12.09.1995 – 14 A 255.95, in: Eberbach/Lange/Ronellenfitsch, Recht der Gentechnik und Biomedizin, Entscheidung Ch. 4 on § 16 GenTG; VG Braunschweig, judgment of 12. 9.1995 – 14 A 255.95, No. 27.

[6] Art. 26a Directive 2001/18/EC; for Germany § 1 No. 2 GenTG.

[7] Thus in a subsidiary argumentation also VG Braunschweig, judgment of 12. 9.1995 – 14 A 255.95, Nos. 31 ff.

[8] See [2] for a forceful pleading in favour of risk-benefit analysis for GMO assessment even in a monetarised form.

[9] For Germany see § 16 paras. 1 und 2 GentG, according to which „harmful effects on the protected goods listed in § 1 No. 1 must not be incurred if unacceptable in view of the objective of the release." Unaccept-

absent in European GMO legislation[10], even though developed more clearly in other areas. For instance, in chemicals legislation, if the risk of a chemical is not adequately controlled or intrinsically very high, an authorisation may nonetheless be granted if the socio-economic benefits outweigh the risk to human health or the environment, and if there are no suitable alternative substances or technologies.[11]

Some kind of consideration of socio-economic benefits has recently been suggested by the EU Council also for GMO policies.[12] When pursuing this request two brands of risk-benefit consideration should be distinguished: a risk-tolerating variant, which, following the highly problematic example of chemicals regulation, would allow any risk that is outweighed by benefits; and a risk-averse variant, according to which only residual risks can be – and must be – outweighed by benefits. An example of the second variant would be the agricultural benefits of certain genetic modifications, e.g. the subsequent non-use of pesticides or the use of less water and chemical fertilizers.Thus, a residual risk to certain parts of the environment could become acceptable, if the overall eco-balance of agriculture were to be improved [4].

2.1.4 Political and moral values

In the past, some Member States, like Austria, Poland and Hungary, counteracted the authorisation of the placing on the market of modified seeds by banning their introduction into the environment. The Austrian Land Upper Austria justified its countrywide ban on the release, among others, with the protection of small farmers. Apart from such agricultural policy, the reasons for the ban can be morally motivated, as in Poland where religious beliefs were cited. Although the European Courts supported the Commission in its measures against Upper Austria and Poland[13], the quarrel between the Member States was not appeased. Looking for a compromise the Commission has proposed amending Directive 2001/18/EC with a new Art. 26(b), which is meant to give Member States more leeway in regulating the cultivation of GMOs on the basis of other criteria than the protection of health and the environment. Unfortunately, the Commission did not reveal which reasons it considers as legitimate.

We believe that, contrary to the Commission proposal, the reasons should lie not outside but within the scope of health and environmental concerns, covering, in particular, national agricultural or nature protection policies. This would entail considering the EU authorisation of GMOs as a partial harmonisation that leaves a margin for supplementary Member State regulation.[14] We would, however, not recommend including moral reasons because – other than with animals – they are hardly justifiable in relation to plants and microorganisms.

2.1.5 Résumé

In summary, it can be said that genetic engineering legislation focuses on human health and the environment as legally protected endpoints. Recently, the coexistence of non-GM agriculture has joined this duo. Hitherto, the assessment of benefits or of political or moral values is not – at least not systematically – acknowledged.

The restriction of scope of legally protected goods also influences the examination and assessment of the risks posed by the release of GMOs: the paths of impact, the GMO model, the generation of knowledge, the distribution of the burden of producing evidence and the assessment of risks are all geared towards risks for human beings, animals and the environment. This is the reason why the rules concerning the required documentation and the risk assessment methodology lack an obligation to submit and assess data about socio-economic costs and benefits as well as political and cultural values.

2.2 Paths of impact

The GMOs introduced into the environment can reach and harm the protected endpoints by different paths. The law determines the relevant ones and attaches control mechanisms, such as a prior authorisation requirement, to them.

Particularly relevant are two paths: the individual release of GMOs, and the cultivation of GMOs

ability in view of the release objective can be understood as a kind of risk-benefit balancing. German scholars tend to reject such interpretation arguing that this would be incompatible with the relevant EU law. See also Art. 10 of the Norwegian Gene Technology Act: " In deciding whether or not to grant an application, considerable weight shall also be given to whether the deliberate release will be of benefit to society and is likely to promote sustainable development." This provision has, however, rarely been applied in practice [3].

[10] See, however, the rather enigmatic opening clause ("... other legitimate factors") in Art. 7 and 19 of Regulation (EC) 1829/2003.

[11] Art. 60 (4) Regulation (EC) No. 1907/2006 of the European Parliament and of the Council of 18.12. 2006 on the reguistration, assessment, authorisation and restriction of chemical substances (REACH), O. J. L 396 of 30.12.2006, p. 1.

[12] Conclusions of the Council 16682/08 of 5.12.2008, No. ii), 7.

[13] See the judgments of the ECJ, T-366/03 and T-235/04 (Land Oberösterreich), Rep. 2005, II-4005; ECJ, C-439/05 P und C-454/05 P (Land Oberösterreich), Rep. 2007, I-714; ECJ, C-165/08 (Commission vs. Poland).

[14] For more fundamental implications in the context of EU multilevel governance see [5] pp. 117 f.

following the placing on the market. The former occurs at identifiable sites and is determined by the authorisation for release; the latter can occur anywhere in the EU and is determined by the authorisation for the placing on the market. For the individual release, three subtypes have emerged: (i) The classical experimental release, which is meant to generate knowledge about the performance and risks of a GMO (it is accordingly confined with regards to the site and number of cases); (ii) a number of trials at the same or at different sites, if sufficient knowledge about the involved risks exists;[15] (iii) a large-scale release at an identified site, such as in the case of the GM-potato Amflora, which was authorised for release and used for the production of seed potatoes [1]. To require in this latter case only an authorisation for individual release rather than for a placing on the market is problematic because some stricter requirements concerning the post-authorisation monitoring applicable for the placing on the market do not apply to deliberate release.[16]

If the GMO is released or cultivated somewhere, the relevant paths of impact diversify further. According to Art 4(3) Directive 2001/18/EC, both direct and indirect effects, the latter occurring through gene transfer from GMOs to other organisms, are to be assessed. An environmental risk assessment (ERA) must evaluate risks "whether direct or indirect, immediate or delayed, which the deliberate release or the placing on the market of GMOs may pose."[17]

The distinction between direct and indirect effects means that not only those adverse effects of GMOs caused by their direct contact with endpoints (e.g. a human being, animal or plant absorbing a GMO) have to be prevented but also those triggered by intervening factors. Annex II of Directive 2001/18/EC defines indirect effects as follows:

> '„indirect effects" refers to effects on human health or the environment occurring through a causal chain of events, through mechanisms such as interactions with other organisms, transfer of genetic material, or changes in use or management.'

By systematising this guideline, one could distinguish between natural causal chains (horizontal and vertical gene transfer, food chain, etc.) and chains mediated by agricultural practices (change in pesticide use and crop rotation, etc.).

Concerning the distinction between immediate and delayed effects, the Commission Guidance on the ERA gives examples for delayed effects such as the GMO developing invasive behaviour after several generations following its release.[18]

In addition to alerting the risk assessment to direct/indirect and immediate/ delayed effects, Directive 2001/18/EC and the Commission Guidance necessitate consideration of different environments exposed to the GMO:

> 'For each adverse effect identified, the consequences for other organisms, populations, species or ecosystems exposed to the GMO have to be evaluated.'[19]
>
> 'Moreover, there may be a broad range of environmental characteristics (site-specific or regional-specific) to be taken into account. To support a case-by-case assessment, it may be useful to classify regional data by habitat area, reflecting aspects of the receiving environment relevant to GMOs (for example, botanical data on the occurrence of wild relatives of GMO plants in different agricultural or natural habitats of Europe).'[20]

While this rather ambitious programme clearly applies to the deliberate release and placing on the market of GMOs covered by Directive 2001/18/EC, it is, by reference[21], also to be applied to GM seed for food and feed. It was further elaborated by the new European Food Safety Agency (EFSA) Guidance of 2010.[22] Specifying the ERA as laid out by Annex II Directive 2001/18 and the related Commission Guidance, the EFSA Guidance distinguishes between the following seven paths of impact:[23]

(1) persistence and invasiveness of the GM plant, or its compatible relatives, including plant-to-plant gene transfer
(2) plant-to-microorganism gene transfer
(3) interaction of the GM plant with target organisms
(4) interaction of the GM plant with non-target organisms
(5) impact of the specific cultivation, management and harvesting techniques

[15] The autorisation is given in a streamlined procedure in this case, see Art. 7 Directive 2001/18/EC.

[16] See also below, section 3.1.3.5). For Amflora the problem of scale for deliberate releases has been solved since it received an authorisation for the placing on the market . See Commission Decision 2010/135/EU, O.J. 2010 L 53, p. 11.

[17] Art 2 (No 8) Directive 2001/18/EC.

[18] Annex to Commission Decision of 24 July 2002 establishing guidance notes supplementing AnnexII to Directive 2001/18/EC ..., O.J. L 200 p. 22, ch. 2.

[19] Commission Guidance (see footnote 18) ch. 4.2.2 para 3.

[20] Commission Guidance (see footnote 18) ch. 3. indent 3 para 4.

[21] Art. 6(4)(1), Art. 7(8) and Art 18(4)(1) Regulation (EC) No. 1829/2003.

[22] EFSA Panel on Genetically Modified Organisms (GMO), Guidance on the environmental risk assessment of genetically modified plants. *EFSA J*. 2010, *8*,1879. Accessible via www.efsa.europa.eu/efsajournal.htm

[23] Each specific path must be considered following the ERA steps (1–6.) mentioned below (section 3.3).

(6) effects on biogeochemical processes
(7) effects on human and animal health

In addition, the EFSA Guidance develops a typology of 'receiving' environments that must be considered.

In conclusion, at the level of the substantive standards for authorisation, the various paths of impact have to be very widely examined. At the level of the data to be submitted by the applicant, however, those standards are not fully implemented. In particular, indirect effects mediated by agricultural practice are not at all mentioned in the list in Annex III, like the changing use of chemicals and the subsequent change in the population of target and non-target organisms or the change in the sources of food available to communities of organisms living on the plant and animal 'enemies' of the cultivated plant. No wonder, therefore, that, as an empirical study shows ([6] p. 97), in the practice of risk assessment data on agricultural indirect effects are hardly ever submitted as part of the application dossier. This shortcoming may be remedied once the new EFSA guidance on the submission of applications for authorisation of genetically modified food and feed and genetically modified plants for food or feed uses under Regulation (EC) No 1829/2003 of 7 July 2011 (*EFSA J*. 2011, *9*, 2311) is applied. Its Annex C lists the data to be submitted including also impacts of the specific cultivation, management and harvesting techniques.

2.3 Biological levels

The natural sciences suggest explaining the behaviour of organisms by several different biological levels encompassing the molecules, cells, individual organisms, communities of organisms, ecosystems and landscapes [7]. Effects on the environment can only be analysed and tuned into a prognosis, if the assertions about environmental effects are based on the knowledge of the interplay of effects at less complex levels.

When looking for the relevant legal framework the scope of the risk assessment and of the data to be submitted should once again be distinguished.

Concerning the scope of risk assessment, the multilevel approach is indeed reflected in the relevant legal acts and the Commission and EFSA guidance papers. The Annex on the ERA particularly emphasises the characteristics of GMOs as well as interactions between the GMO and other organisms.[24] The level of landscapes is, however, not mentioned. Neither is there a requirement for an in-depth analysis on the molecular and cellular levels.[25]

Concerning the submission of data, the multilevel approach has been more clearly adopted by the relevant law. This is visible in the list of information to be supplied with applications for the deliberate release and the placing on the market of GMOs[26]:

- Molecular and cellular level[27]:
  1. Description of the trait(s) and characteristics that have been introduced or modified
  2. Information on the sequences actually inserted/deleted
  3. Information on the expression of the insert
- Level of organism and level of population:
  4. Information on how the GM (higher) plant (GMHP) differs from the recipient plant in:
     (a) mode(s) and/or rate of reproduction;
     (b) dissemination;
     (c) survivability
  5. Genetic stability of the insert and phenotypic stability of the GMHP
  6. Any change to the ability of the GMHP to transfer genetic material to other organisms
  7. Information on any toxic, allergenic or other harmful effects on human health arising from the genetic modification
  8. Information on the safety of the GMHP to animal health
- Level of the ecosystem:
  9. Mechanism of interaction between the GMHP and target organisms (if applicable)
  10. Potential changes in the interactions of the GMHP with non-target organisms resulting from the genetic modification
  11. Potential interactions with the abiotic environment
- Technical information:
  12. Description of detection and identification techniques for the GMHP
  13. Information about previous releases of the GMHP, if applicable

It appears that information on all biological levels is asked for. However, information on the affected ecosystem and landscape is only required for deliberate release at a predetermined location, not on types of ecosystems and landscapes where the

[24] Annex II to Directive 2001/18/EC, ch. C. and D.

[25] The flaw on the level of regulation is reflected in the actual risk assessment practice. For instance, while insecticide effects of insecticide GMOs are checked this is not the case with effects of other biochemical substances such as protein/ toxin metabolites of Bt which may be produced by the modified GMO. See [6, pp. 64, 159, 229].

[26] Annex III B to Directive 2001/18/EC, ch. D.

[27] This and the following headings were added by the authors.

GMO may be released after being placed on the market.[28]

2.4 The starting point of risk causation

The risks of a GMO can be caused by traits of the non-modified parental line and of the genetic modification. The concept of familiarity (or – using about the same approach – comparison with similar organisms or substantial equivalence), which goes back to an OECD paper of 1993 [8], suggests that only effects of the genetic modification should be assessed. This is reasonable because otherwise the applicant could be blamed for adverse effects that are already contained in the parental line. However, critiques have alleged that, by focussing on the modification, the concept of familiarity cuts the organism into pieces and disregards effects of the new entire organism. Rather than assuming firm knowledge of the unmodified organism, one should rather look for the unexpected, the unfamiliar [9].

Asking what the law demands in this regard, it should first of all be noted that the concept of familiarity is not conveyed by the wording of the substantive standard expressed in Directive 2001/18/EC. Rather, its Art. 4(1) says comprehensively that the release and the placing on the market of the GMO must not cause any adverse effects. The annexed rules on the ERA, however, state that a comparison with non-modified organisms "will assist in identifying the particular potential adverse effects arising from the genetic modification."[29] The new EFSA Guidance of 2010 unduely reinforces this approach by making the 'comparative safety assessment' the core yardstick of risk assessment.[30]

Whether called comparative or not, in any case the examination is not allowed to imply that the transgene has to be considered in isolation. Unintended position effects and mutual reactions at all organismic levels are rather the consequence of genetic modifications and have to be considered to their full extent. Upon closer look this is also envisaged by the EFSA Guidance of 2010.[31] Therefore, the Annex on ERA is still right to regard the comparative approach as a heuristic rather constitutive tool of the risk assessment.

3 Steps of examination and assessment

Not only the object of risk assessment but also the risk assessment itself as a process must be structured. The structuring concerns the generation, the submission and the assessment of risk-related knowledge.

3.1 Stepwise generation of knowledge (step-by-step principle)

3.1.1 Introduction

Towards the end of the 1980s when the deliberate release of GMOs was approached, knowledge about the involved risks was still highly undeveloped. Even now many knowledge gaps have prevailed. Nonetheless, to enable releases and acquire knowledge, the step-by-step principle was introduced: incremental generation of knowledge in parallel with decreasing containment of tests.[32] The principle is characterised by recitals (24) and (25) of Directive 2001/18/EC as follows:

> 'The introduction of GMOs into the environment should be carried out according to the 'step by step' principle. This means that the containment of GMOs is reduced and the scale of release increased gradually, step by step, but only if evaluation of the earlier steps in terms of protection of human health and the environment indicates that the next step can be taken. No GMOs, as or in products, intended for deliberate release are to be considered for placing on the market without first having been subjected to satisfactory field testing at the research and development stage in ecosystems which could be affected by their use.'

In the following, the binding force and the material content of the step-by-step principle are clarified.

3.1.2 Binding character of the step-by-step principle

Recital (24) introduces the principle merely as a directory provision. In contrast, the step-by-step principle is not mentioned as a substantive standard in either Directive 2001/18/EC or Regulation (EC) No. 1829/2003. It is only alluded to in connection with the submission of data, in so far as the applicant has to submit "information about previous releases of the genetically modified plant, if applicable".[33] This is reminiscent of the risk assessment,

[28] Annex III B to Directive 2001/18/EC ch. E.

[29] Annex II Directive 2001/18/EC, C. (see section 2.1).

[30] EFSA Guidance (above footnote. 22) ch. 2.1.

[31] EFSA Guidance (above footnote. 22) ch. 2.1. nos. 1–4.

[32] The step-by-step procedure goes back to OECD reports, including OECD, Safety considerations for biotechnology, 1992 (available at www.oecd.org/dataoecd/8/3/2375496.pdf).

[33] Annex III B of Directive 2001/18/EC, D 13; similar Annex III, A. II. C. 2. h and III. A. 11.

since the latter takes into consideration earlier releases as material for the prognosis of cumulative long-term effects.[34]

Although the step-by-step principle is not explicitly mentioned as a substantive standard and can, therefore, not be considered as a strict requirement for authorisation, it does have some substantive significance as a guideline for interpretation. When Art 4(1) Directive 2001/18/EC asks the Member States to "ensure that all appropriate measures are taken to avoid adverse effects", this means, under inclusion of recital 24, that not 'all appropriate measures' were taken, if a risk arises that could have been investigated at a previous step. The fact that the recital uses the word "should" means that step-by-step is to be followed as a rule allowing for reasonable exceptions.

In contrast to this – qualified – binding character, an examination of the practice of dossiers submitted to proceedings under Regulation (EC) No. 1829/2003 by the StepKo Project reveals that for many required data no pre-stage tests were conducted. Quite often references are made to the literature or trials of other applicants without sufficient proof that the findings are comparable. This means that part of the submitted information is not reliable or not valid, and that, insofar as the later stage is used to generate the lacking information, this entails additional and avoidable environmental risk [10].

3.1.3 Substance of the step-by-step principle

The following sequence of steps has emerged in practice:

- laboratory
- greenhouse
- small-scale release with strict containment (not specified in law)
- larger-scale release with more relaxed containment
- placing on the market[35]
- subsequent measures covered by the authorisation
- subsequent Member State measures based on safeguard clause

The content of the individual steps and their interrelations are as follows.

3.1.3.1 Knowledge generation at earlier steps

The substance of the step-by-step principle has been somewhat specified by the Commission Guidance, which says that "data from each step should be collected as early as possible during the procedure." It points to the possibility that "simulated environmental conditions in a contained system could give results of relevance to deliberate release", such as the simulation of the behaviour of microorganisms in the laboratory and of plants in greenhouses.[36]

If at a given step data are missing that could have been generated at earlier steps, the relegation to a previous stage is admissible. However, this is not allowed if the relegation is to inquire merely into speculative risks.

3.1.3.2 Inferences from previous to subsequent steps

A core issue of the step-by-step stages approach is whether the data of one stage potentially render subsequent examinations at the next stage unnecessary. In the proceedings concerning the 1507xNK603 maize, the applicant argued, for instance[37]:

> "The specificity of the biological activity and the absence of toxicity to non-target organisms of the proteins CRY1F, PAT and CP4 EPSPS confirm that there will be no adverse effects on non-target organisms arising from 1507xNK603 maize."

This means that the applicant in his/her application dossier infers from the organismic level (namely from the claimed characteristic of a GMO to be toxic only for specific target organisms) to the level of communities of organisms, concluding that additional trials at this level are unnecessary. However, this was heavily criticised during the commenting procedure by other Member States, which demanded independent trials concerning the interaction of the GMO with a number of non-target organisms.

3.1.3.3 Toleration of risks in case of inappropriate testing in previous step

The experimental release of a GMO does, on the one hand, serve to generate information about risks but, on the other, it may pose a risk itself if the relevant knowledge could not be obtained from tests in closed systems. The control of GMOs is, therefore, confronted with the dilemma that the authori-

[34] See Commission Guidance (footnote. 18), end of ch. 3: „In considering the potential cumulative long-term effects, the ERA should take into account issues such as: [...] the GMOs deliberately released or placed on the market in the past."

[35] The placing on the market should be subcategorised into one step with highly restrictive and one with less restrictive use conditions.

[36] Commission Guidance (footnote 18) ch. 3.

[37] Analysis by the authors of the initial technical dossier from the applicant as submitted to EFSA. The dossier is still under assessment.

Biotechnol. J. 2012, 7, 569–581

sation of a trial sometimes presupposes its very findings. To avoid a vicious circle, preventing any introduction of a GMO into the environment, a pragmatic approach is necessary that minimises risks and generates at the same time knowledge about risks.

This was also highlighted by the German Federal Constitutional Court in a recent judgement. The court considered such risks as an unavoidable implication of the constitutional freedom of research. They had to be tolerated by colliding interests that are likewise protected by the constitution (like environmental protection and property rights of non-GMO farmers). On the other side, the court ruled that a balanced compromise of research and other interests also includes that science can be held accountable for minimizing risks and liable to compensate any damage caused by it.[38]

3.1.3.4 Requesting trials at the pre-stages

It is an aspect of the mentioned dilemma that trials at an earlier stage (e.g. deliberate release; let us call it level I) are necessary to generate data for a subsequent level (e.g. placing on the market; let us call it level II), but that the authorities are not allowed to request certain series of tests that are insignificant for the safety of level I but become relevant for level II. At level I, the authorities can only evaluate whether the submitted information considers the risks of level I sufficiently.

To give an example: at level I (deliberate release) the risk of pollen flight exists, which assumedly can be minimised by sowing a safety margin around the seeds. If an authority requires an applicant to do this for safety reasons at level I, it can not at the same time order the applicant to scientifically investigate the flying qualities of the pollen. For that no legal basis exists. However, for level II (placing on the market) data about pollination are essential, since the authorities can hardly link the authorisation of the placing on the market with the condition of growing a safety margin around any cultivation. At level II, they can only request that data about the flight of pollen are presented.[39]

It would be only fair if the applicant were at an early stage able to match his studies and examinations with the sequence of required data. Therefore, the development of two kinds of guidelines are conceivable: (1) A (binding) guideline, which clearly states what data have to be submitted at a certain stage to guarantee the safety of this same stage; (2) a (non-binding) guideline advising what data should be generated at a given stage to prepare an application for the subsequent stage.

If the suggested guidelines were available to the applicant, she/he could better prepare future applications. In this way, it would be possible to avoid postponing collection of data that could have been generated in the glasshouse, like those concerning the morphology and physiology of the plant, until the release trial, or that data, which could be generated in release trials, are missing in applications for the permission to placing on the market.

3.1.3.5 Monitoring as a stage of knowledge generation

The step-by-step principle is an instrument of societal learning. In the initial phase of European genetic engineering legislation, it was at the fore of the public debate and became a legal requirement as outlined. With the amendment through Directive 2001/18/EC, monitoring has become an additional instrument. In order to increase safety and at the same time facilitate the release and the placing on the market of GMOs, it was emphasized that those issues that for reasons of time or scale could not be solved at one level can be clarified through monitoring at the next level. Monitoring can, therefore, be seen as a phase of social learning following the release or the placing on the market, respectively. In particular, this concerns the investigation of effects that cannot be researched on an experimental basis, such as complex interactions on the population and ecosystem levels, cumulative and long-term effects and effects at the landscape and regional level, all the more so because experiments on such levels are not feasible for political or ethical reasons.

Two forms of monitoring are envisaged: general surveillance and case-specific monitoring. Case-specific monitoring is meant to examine the assertions of the risk assessment with regard to the effects of the GMO. The general surveillance is in turn meant to reveal adverse effects which were not covered by the risk assessment. This concerns especially indirect, cumulative and long-term effects, which are naturally hard to predict. The obligation to monitor also entails the applicant informing the competent authorities about the findings.[40]

[38] BVerfG, judgement of 25.11.2010, 1 BvF 2/10, nos. 310, 312, 313 (available at www.bverfg.de/entscheidungen/fs20101124_1bvf000205.htm).

[39] Of course, it would also not be possible to grant authorisation and leave the issue of cross-pollination to the monitoring phase.

[40] Art. 20 Directive 2001/18/EC.

The design, organising institution and cost responsibility of monitoring cannot be outlined here.[41] In the given context of the step-by-step principle, it is sufficient to stress that the findings of the case-specific and the general monitoring may lead to a number of additional steps: if unacceptable risks are detected, the revocation of the authorisation and the rejection of applications for prolongation of authorisations, and if the results are negative the issuance or prolongation of an authorisation.

3.2 Burden sharing in the provision of data

As mentioned above, a risk prediction is only possible if sufficient data are available. Generally, in administrative proceedings the authorities are responsible for collecting the relevant data (investigation principle).[42] Ultimately, this rule rests on the fundamental right to freedom of the individual, which implies that if a law imposes restrictions under certain factual circumstances these facts must be identified and proven by the competent authority.

3.2.1 Data provision by the applicant

The burden of producing evidence can, however, be imposed on the individual by special legislation. This normally occurs if an activity requires prior authorisation, because it is assumed that the activity poses a societal problem and can, therefore, only be authorised after detailed examination. Such a case is also the introduction of GMOs into the environment. It is in both its variants, experimental release and placing on the market, considered to pose potential risks. The European and national legislations therefore shift the burden of data provision to the applicant.

The mentioned legislations specify which data have to be presented. Under fundamental rights, the scope of the data has to be guided by the substantive protective standard justifying intrusions in fundamental freedoms – the prevention of adverse effects on human health, the environment and material assets. Data concerning societal benefits can only be requested if the law is interpreted to entail a risk-benefit weighing (see above 2.1.3).

If the presented data are not sufficient to allow a prognostic assessment, the competent authority can request the submission of additional data. Although this is not explicitly formulated in Directive 2001/18/EC – in contrast to the legislation for chemicals[43] – it is nevertheless implied in the power of the competent authority to reject an application if it cannot be assured that no adverse effects will occur. If sufficient knowledge is not available to assess this, the applicant bears the burden of generating it if the application is not to be rejected.

3.2.2 References to existing knowledge

Knowledge relevant for an authorisation proceeding may already be held by the administrative authority. If that is the case, the authority must make use of it in the authorisation procedure and cannot ask the applicant to reproduce it anew. The authority is hindered in using the data, in order to prevent unfair competition, only if it was submitted by a previous applicant for authorisation of the same GMO. In this case, the second applicant must seek approval by the first.[44] If the approval is not given, the second applicant has to provide the data.

Relevant knowledge may also be brought in by authorities of other Member States. Since the decision about deliberate release and placing on the market has significance across borders – as released GMOs can have effects in neighbouring countries, and the placing on the market can occur in them – the competent authorities of the other Member States are given the opportunity to comment on an application during the authorisation procedure. Our study of two example cases established that comments are made particularly often in proceedings concerning the placing of a GMO for cultivation on the market.[45] The main objections we found alleged a lack of studies on the level of the communities of organisms and ecosystems. The applicant can in principle refer to existing published information instead of generating it anew. However, the information referred to must be taken from studies that are valid and reliable. In this context, the case-by-case principle must be kept in mind,[46] which suggests that every GMO release is generally unique.

Research on the procedural practice established that these requirements of the comparability of tri-

[41] See also Annex VII of Directive 2001/18/EC, the related Commission Guidance (see footnote. 22 above) and Opinion of the Scientific Panel on Genetically Modified Organisms on the Post Market Environmental Monitoring (PMEM) of genetically modified plants. *EFSA J.* 2006, *319*, 1–27; available at http://www.efsa.europa.eu/en/efsajournal/pub/319.htm. See also [11].

[42] For Germany see Art. 24 Administrative Procedure Act (VerwVfG).

[43] Cf. Art. 46 und Art. 64 Abs. 5 Regulation (EC) 1907/06.

[44] Art. 6 (3) Directive 2001/18/EC.

[45] The authors analysed the dossiers on the authorization procedures for a potato variety programmed to produce altered starch composition (amylopectin) (called Amflora) and for a maize variety made both herbicide resistent and insecticide (called Maize1507 X NK603).

[46] Art. 4 (3) Directive 2001/18/EC.

als are often not observed. Although almost all examined dossiers included findings from field trials with non-target organisms, these findings were often only quoted but not attached. Sometimes, findings from studies with the specified organism were missing; in such cases, reference was instead made to a comparable organism. Furthermore, often the site or country in which the trials were conducted, or what trial design and methods were used, were not indicated.[47]

3.2.3 Standardisation

Confronted with a generally infinite need for information, it would be a help to the applicant if the required information were more standardised. In contrast to the chemicals legislation, the genetic engineering legislation contains neither standardised criteria of dangerousness nor standardised methods of research into the characteristics and interactions of the GMO. It is merely required that the applicant reveals the applied methods.[48] As a matter of fact, due to the novelty of genetic engineering the state of knowledge is hardly sufficient to allow much standardisation.[49] In any case, standardisation would need to find a middle course between the generally infinite scientific process of inquiry and economically reasonable costs.

The new EU pesticide Regulation (EC) No 1107/2009 can provide a model for the development of such a piece of legislation. It requests all applicants to present precise information about conducted studies required for the risk assessment. They have to submit a fix catalogue of proofs (among others about the fate and behaviour in the environment, the toxicological significance, the impact on human health and the environment), and the methods of analysis have to meet recognised guidelines. Furthermore, the applicant has to inform the authorities about the state of the relevant literature:

> 'Scientific peer-reviewed open literature, as determined by the Authority, on the active substance and its relevant metabolites dealing with side effects on health, the environment and non-target species and published within the last 10 years before the date of submission of the dossier shall be added by the applicant to the dossier.'[50]

The development of such standards for the application of GMO trials could enhance both the equal treatment of the applicants as well as the verifiability of data. Overall the application procedure would be more comprehensible, and sources of error more easily identified.

3.3 Steps in the analysis and assessment of risks

The information presented by the applicant does not allow direct legal consequences to be derived. The simple judicial syllogism ('if A, then X. A is given. Therefore X follows.') would not do justice to the fact that the presented data have to be evaluated before a decision can be made on whether adverse effects can be expected. This intermediate step consists of the ERA.

The ERA regarding the authorisation of a GMO must observe the precautionary principle.[51] This allows extending the examination to subject matters whose potential adverse effects remain unclear. It is, however, necessary that there are clues for such risks; 'a purely hypothetical approach to the risk' is not sufficient.[52] If such clues exist, there is, according to the wording of Art 4(1) Dir 2001/18/EC, not only the power but also the obligation to consider such clues and hence also to examine them.

It is characteristic for the risk assessment in form of the ERA that it processes the data successively in pre-defined steps. The staggered evaluation of risks is finally followed by the risk management, which translates the scientifically informed risk evaluation into measures, i.e. the authorisation, the conditions for the authorisation and, if applicable, the rejection of authorisation.

The ERA as outlined by Annex II Directive 2001/18/EC focuses on those paths of risk with human health and the environment as endpoints. Other endpoints, like the coexistence with non-GM agriculture, the economic benefit and political as

[47] For more detailed information on the analysis of the procedural practice see [6].

[48] See the introduction to Annex III Directive 2001/18/EC: "The description of the methods used or the reference to standardised or internationally recognised methods shall also be mentioned in the dossier, together with the name of the body or bodies responsible for carrying out the studies."

[49] Currently the European Commission, together with the Member States are in the process of defining more specific standards for risk assessment, as was required by the Council in 2008 (see footnote. 12 above).

[50] Art. 8 (5) Regulation (EC) 1107/2010.

[51] Art. 4 (1) Directive 2001/18/EC.

[52] ECI, judgement of 11.9.2002, Case T-13/99, No. 143. The court stipulates that "a preventive measure may be taken only if the risk, although the reality and extent thereof have not been 'fully' demonstrated by conclusive scientific evidence, appears nevertheless to be adequately backed up by the scientific data available at the time when the measure was taken." (No. 144). See also Commission Communication on the precautionary principle, Com(2000) 1, p. 8, where while uncertainty is acknowledged as basis for taking measures "indications" for adverse effects are nonetheless called for.

well as cultural values, are hardly considered. However, should these aspects be interpreted to be or introduced as a legally required part of the risk management, then information would have to be provided and assessed which is methodologically clear and rich in substance.[53]

According to Annex II of Directive 2001/18/EC and the respective Commission Guidance, the ERA consists of six steps.

In step 1, the inherent characteristics of the GMO are to be identified. These hazards, as they are called, present factors that can lead to risks depending on environmental conditions and usage.[54]

In step 2, the potential consequences of each established hazard trajectory have to be evaluated. The evaluation concerns organisms, populations, species and ecosystems interacting with the GMO. Particular emphasis is given to the expected magnitude of the consequences. The latter can depend on the genetic design, the established adverse effects, the number of released GMOs, the receiving environment, the manner of the release and the control measures taken, as well as on a combination of all these factors. The evaluation of adverse effects is conducted by applying four categories – 'high', 'moderate', 'low' and 'negligible'.

In step 3, the likelihood of the occurrence of each identified potential adverse effect is to be evaluated; here, each effect is examined individually, taking into account the risk factors, the number of released GMOs, the likelihood and frequency of gene transfer, the receiving environment and the conditions of the release. The likelihood of the occurrence of every consequence is to be categorised as 'high', 'moderate', 'low' or 'negligible', while a precise quantitative evaluation is not envisaged.

In step 4, the different magnitudes of consequences (high, moderate, low, negligible) of every risk factor are linked to the different degrees of their likelihood (high, moderate, low, negligible). In addition, the overall uncertainty for each identified risk has to be described, including assumptions and extrapolations made at previous levels in the ERA, different scientific assessments and viewpoints, and the uncertainties contained in each evaluation.

In step 5, management strategies for risks from the deliberate release (or marketing) of GMOs are to be developed. The risk management is to be designed in a way so that identified risks can be controlled and that uncertainties can be covered. Safeguarding measures (coated seeds, isolation distances, etc.) have to be proportionate to the levels of risk and uncertainty.

In step 6, the overall risk of the GMO is determined. This consists of a summary of all identified risks and uncertainties of the examined application, taking into account the magnitude and likelihood of the adverse effects as well as the previous release of other GMOs. The achieved risk reduction caused by the management measures has also to be considered.

Evaluating the ERA methodology, it is striking that the ERA is modelled after the classical scheme of risk assessment for chemicals. However, it is doubtful whether such similarity does justice to the differences between risks from chemicals and GMOs. It would be necessary to discuss whether the distinction between the intrinsic characteristics of substances (hazard assessment) and their exposure conditions (exposure assessment), central to the assessment of chemicals, can be applied to GMOs, or whether it is more appropriate to think in terms of error trees and event trees, in which characteristics, release conditions, impact paths and impact modes are conceived as complex chains [12].

Moreover, the concept of assessment steps hardly corresponds with the biological levels approach discussed above. Imaginably, the molecular, cellular and organismic levels are processed at the first step (hazard identification) and the levels of organismic interactions, ecosystems and landscapes at the second, third and fourth (kinds, magnitude and likelihood of effects). However, hazards may well result from higher levels than the organismic, and, vice versa, the assessment of the likelihood of effects may necessitate a specific molecular analysis. Therefore, a different staggering of risk assessment might be considered that takes the biological levels approach as a guideline and considers effects and likelihood on each of the levels.

From a legal perspective, it should be stressed that the results of the ERA have finally to be evaluated according to legal standards. If the risk assessment comes to the conclusion that a risk is 'high', 'moderate', 'low' or 'negligible', this does not, in legal terms, mean that the authorisation of release has to be refused or granted. The expert assessments must be subsumed under the legal term 'adverse effects on the environment'. In view of the precautionary principle risk must be minimized. It does not, however, have to be absolutely excluded: a residual risk must be tolerated. This is justified,

[53] An elaborate (albeit problematic, see above 2.1.3) example in that respect is the socio-economic analysis which is to be submitted according to Art. 62 (5) Regulation (EC) 1907/06.

[54] It is unclear if 'hazard' means the intrinsic potentially adverse properties of an organism or the preliminary scoping of potential consequences and their likelihood. See further [13].

on the one hand, by the confines of human cognitive faculty and, on the other, by the fact that the perfection of risk reduction can come at the expense of other goods.[55] Regarding the last aspect, the authors argue that existing residual risks are only tolerable, if they are offset by a benefit. In the phase of experimental release, the latter would be constituted by scientific progress, and at the level of placing on the market, it would consist of an agro-ecological benefit gained by the use of genetic engineering.[56]

4 Summary

The deliberate introduction of GMOs into the environment triggers complex biological processes. They have to be understood and assessed to allow a justified decision about its authorisation to be made. Such complex phenomena can in their entirety not be grasped at once. They have to be dissected into individual dimensions, which can then be examined and assessed in well-ordered steps.

This essay has shown that this substantive and procedural differentiation and reconstruction is laid out in specific ways by the relevant legislation. In relation to the object of assessment, the law determines the goods protected by law as well as the paths of impact, the biological levels and the relevant source of risk causation, that are to be considered. In relation to the examination procedure, it structures the generation of risk knowledge, the distribution of the burden of producing evidence and the tiers of risk assessment.

The disjunction of the object of inquiry is reassembled in the overarching standard that the release of a GMO as a whole – in its facets of endpoints, paths of impact, biological levels and causative factors – must not induce any adverse effect to human health and the environment. The disjunction of the examination procedure is, at the end of a step-by-step accumulation of knowledge, a structured distribution of the burden of producing evidence and the tiers of risk assessment, summarised in an overall judgement on the resulting risks.

The law leaves the risk assessment primarily to scientific expertise sought by the competent authorities; however, it also establishes confines by the very stipulation of reasonable disjunction and recombination.

This article is an outcome of an interdisciplinary research project funded by the German Federal Agency for Nature Protection (German Bundesamt für Naturschutz, BfN) on the step-by-step-principle in GMO risk assessment. We are grateful for helpful comments to Broder Breckling, Angelika Hilbeck and Andreas Lang on the side of the project partners, Andreas Heym, Beatrix Tappeser, Birgit Winkel and Wiebke Züghart on that of the mandator, as well as to the two anonymous reviewers. The views expressed by the authors do not necessarily reflect those of the BfN. A previous version of this text appeared in German in Zeitschrift für Umweltrecht *5/2011, pp. 227-240.*

The authors declare no conflict of interest.

5 References

[1] Morrow, K., Genetically modified organisms and risk, in: Bodiguel, L., Cardwell, M. (eds.), *The regulation of genetically modified organisms: comparative approaches*, Oxford University Press 2010, pp 54–76.

[2] Charlier, C., Valschecini, E., The importance and limits of cost-benefit analysis in the regulation of genetically modified organisms, in: Bodiguel, L., Cardwell, M. (eds.), *The regulation of genetically modified organisms: comparative approaches*, Oxford University Press, Oxford 2010, pp 37–53.

[3] Spök, A., *Assessing socio-economic impacts of GMOs*, Bundesministerium für Gesundheit, Wien 2010. http://www.bmg.gv.at/cms/site/attachments/2/7/6/CH0808/CMS1287125505520/assessing_socio-economic_impacts_of_gmos,_band_2_2010.pdf, (visited 27.12.2010).

[4] Winter, G., Nature protection and the introduction into the environment of genetically modified organisms: Risk analysis in EC multilevel governance. RECIEL, 2008, 17, 205–220.

[5] Lee, M., Multi-level governance of genetically modified organisms in the European Union: Ambiguity and hierarchy, in: Bodiguel, L., Cardwell, M. (eds.), *The regulation of genetically modified organisms: comparative approaches*, Oxford University Press, Oxford 2010, pp 101–122.

[6] Dolezel, M., Miklau, M., Eckerstorfer, M., Hilbeck, A. et al., *Standardising the environmental risk assessment of genetically modified plants in the EU*, Bundesamt für Naturschutz, Bonn, BfN-Skripten 259/ 2009.

[7] Breckling, B., Dolek, M., Lang, A., Reuter, H., Verhoeven, R., *Die ökologischen Organisationsebenen als Kriterium der Übersicht und Vollständigkeit im GVO Monitoring,* in: Breckling, B. Dolek, M., Lang, A., Reuter, H., Verhoeven R. (eds.), *GVO Monitoring vor der Umsetzung*. Naturschutz und biologische Vielfalt 49/2007, pp 227–243.

[8] OECD, Safety evaluation of foods derived by modern biotechnology. Concepts and principles, 1993.

[9] Breckling, B., Naturwissenschaftliche Grundlagen der Gentechnik als Ausgangspunkt zur Risikoabschätzung gentechnisch veränderter Organismen, in: Umweltbundesamt (ed.) *Fortschreibung des Konzepts zur Bewertung von Risiken bei Freisetzungen und dem Inverkehrbringen von GVO*, Berichte 3/04, E. Schmidt Verlag Berlin 2004, pp 52–59.

[55] This was aptly expressed by the German constitutional court in its judgement on a nuclear fast breeder reactor, Case 2 BvL 8/77 (Kalkar), BVerfGE 49, pp. 89 ff. (143).

[56] See above section 2.1.3.

[10] Breckling, B. (ed.), A Modular Concept for the Step-by-Step-Principle, Final Report of the StepKo Project, commissioned by Bundesamt für Naturschutz (FKZ 350789050), Draft of June 2011, on file with authors, ch. 2.2.and 2.3.

[11] Züghart, W., Raps, A., Wust-Saucy, A.-G., Dolezel, M., Eckerstorfer, M., *Monitoring of genetically modified organisms*, A policy paper representing the view of the National Environment Agencies in Austria and Switzerland and the Federal Agency for Nature Conservation in Germany, Environment Agency Austria, Report REP 0305, Vienna 2011.

[12] US National Research Council, *Risk assessment models: Environmental effects of transgenic plants – The scope and adequacy of regulation*, National Academy Press, Washington DC, pp 93–100.

[13] Hill, R. A. Conceptualizing risk assesment methodology for genetically modified organisms, *Environ. Biosafety Res.* 2005, *4*, 67–70.

